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EXAMINER	
STRZELECKA, TERESA E	
ART UNIT	**PAPER NUMBER**
1637	

DATE MAILED: 03/17/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/943,416	LIU, XIANGJUN	
	Examiner	Art Unit	
	Teresa E Strzelecka	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 January 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *22-39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. This office action is in response to an amendment filed January 4, 2005. Claims 22-39 were previously pending. Applicant amended claim 22. Claims 22-39 are pending and will be examined.

2. Applicant's amendments and arguments did not overcome any of the previously presented rejections. Response to Applicant's arguments is presented in the "Response to Arguments" section below.

Response to Arguments

3. Applicant's arguments filed January 4, 2005 have been fully considered but they are not persuasive.

A) Regarding examiner's interpretation of the term "random bases" as meaning any bases, since the definition of the term was not provided by Applicant, Applicant argues that "random" means any bases but the ones which are complementary to the target. However, this definition was not provided by Applicant in the specification, therefore, the broadest reasonable interpretation of the term is the one presented by examiner. As to the use of the dictionary term for "random", it is totally inappropriate in the context of nucleic acids. Further, as pointed out above, the guidelines for examination and claim interpretation are provided by MPEP 2111.01:

> **2111.01 Plain Meaning [R-2]**
>
> **I. THE WORDS OF A CLAIM MUST BE GIVEN THEIR "PLAIN MEANING" UNLESS THEY ARE DEFINED IN THE SPECIFICATION**
>
> While the claims of issued patents are interpreted in light of the specification, prosecution history, prior art and other claims, this is not the mode of claim interpretation to be applied during examination. During examination, the claims must be interpreted as broadly as their terms reasonably allow. >*In re American Academy of Science Tech Center*, ___ F.3d ___, 2004 WL 1067528 (Fed. Cir. May 13, 2004)(The USPTO uses a different standard for construing claims than that used by district courts; during examination the USPTO must give claims their broadest reasonable interpretation.).< This means that the words of the claim must be given their plain meaning unless applicant has provided a clear definition in the

specification. *In re Zletz*, 893 F.2d 319, 321, 13 USPQ2d 1320, 1322 (Fed. Cir. 1989) (discussed below)**>; *Chef America, Inc. v. Lamb-Weston, Inc.*, 358 F.3d 1371, 1372, 69 USPQ2d 1857 (Fed. Cir. 2004)

Therefore, since Applicant did not define the term "random bases" in the specification, the term is given it's "plain meaning" in the art, as meaning any nucleic acid base.

B) Regarding the written description rejection of claims 18, 19 and 21-23 under 35 U.S.C. 112, first paragraph, over the limitation of "...wherein complementary regions of the oligonucleotides flank the spacer, further wherein the complementary regions of the oligonucleotides hybridize with a contiguous sequence on the target oligonucleotide..." not being supported by the specification, Applicants argue that this limitation inherently follows from two parts of the disclosure, namely, paragraph [0069], where probes with random oligonucleotides in the middle are disclosed, and from paragraph [0068], where probes with perfect complementarity to the target were disclosed.

However, these were two different sets of probes (emphasis added). There is no mention of the sequence complementarity or hybridization targets of the regions flanking the middle region of probes in paragraph [0069], therefore, there is no basis for this limitation in the specification.

The rejection is maintained.

C) Regarding the rejection of claims 22-31, 33-37 and 39 under 35 U.S.C. 103(a) over Armstrong et al., Van Ness et al. and Lee et al., Applicant argues that there is no motivation to combine Lee et al. with Armstrong et al. and Van Ness et al., since the oligonucleotides of Lee et al. are primers, whereas, as stated by Applicant "In contrast, the method of Armstrong et al. is purely based upon hybridization of the probe to a target sequence without production of an extension product in a PCR reaction. The hybridization probes of Armstrong et al. are never used as primers in the polymerase chain reaction. Thus, Lee et al. and Armstrong et al. refer to different types of

technology." Similar arguments is provided for lack of motivation of combining Van Ness et al. and Lee et al., Applicant citing the fact that Van Ness et al. state that the spacer cannot enter into hydrogen bonding with other bases.

However, Applicant is first reminded that a primer is a probe, which can further serve as means for duplicating the template by a polymerase. As is very well known by everyone in the art, the specificity of the primer hybridization to the target is critical for the successful target amplification. Therefore, by teaching increase in the specificity of primer hybridization through the use of primers with internal spacers, Lee et al. teach ways to increase specificity of the hybridization reaction, which would be recognized by anyone in the art, since this is the same technology. Therefore, there is ample motivation to combine the teachings of Armstrong et al. and Lee et al. As to the combination of Van Ness et al. and Lee et al., the statement "the spacer cannot enter into hydrogen bonding with a base positioned opposite itself in a hybridized complementary base sequence" can also mean that the bases can be "natural", as used by Applicant, but cannot enter into hydrogen bonding with the bases on the opposite strand simply because they are not complementary to those bases. Even if Van Ness et al. specifically stated that the spacer has to be a nucleic acid with "unnatural" bases, it does not make any difference in the obviousness analysis of the instant claims, since the reference of Van Ness et al. is used to provide the idea of increasing hybrization specificity in the sequences containing spacers, and since the oligonucleotides of Lee et al. contain such spacers, there is a very good motivation to combine these references as well.

The rejection is maintained.

D) Regarding the rejections of claims 32 and 38 under 35 U.S.C. 103(a) over Armstrong et al., Van Ness et al. and Lee et al., in view of Fulton et al., Applicant argues that there is no motivation to combine Armstrong et al., Van Ness et al. and Lee et al., therefore there would be no

motivation to combine Fulton et al. with these references. The argument about combining Armstrong et al., Van Ness et al. and Lee et al. has been addressed above.

The rejection is maintained.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 22-39 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The limitation "...wherein complementary regions of the oligonucleotides flank the spacer, further wherein the complementary regions of the oligonucleotides hybridize with a contiguous sequence on the target oligonucleotide to provide perfect sequence homology between the complementary regions of the oligonucleotide and the contiguous sequence of the target oligonucleotide", added to claim 22 in the amendment filed July 19, 2004 and January 4, 2005, is not supported by the disclosure of the instant application. Applicant points to paragraphs [0068]-[0070] as containing the support for the added limitation. However, inspection of these paragraphs shows that the only embodiment Applicant contemplated were oligonucleotides with a spacer of 20 random bases in the middle of an oligonucleotide sequence in paragraph [0069]. There is no disclosure of the spacer being flanked by complementary regions which hybridize to a contiguous sequence on the target oligonucleotide, or the perfect sequence complementarity between the flanking regions and the target.

Therefore the added limitation constitutes new matter.

Claim interpretation

6. As indicated by Applicants, the interpretation of the limitation in claim 22: "wherein the oligonucleotides that are coupled to different bead sets are oligonucleotides with and without a spacer", is that "all combinations of oligonucleotides with and without spacers coupled to bead sets are permissible in the claimed invention so long as the claimed method can be effectively performed" (Reply, page 16, third paragraph).

7. The limitation "a bead set", not defined by Applicant, is interpreted as: 1) two or more beads bound to the same type of oligonucleotide (For example, if oligonucleotide A has a different sequence from oligonucleotide B and both of them are coupled to beads, there are two bead sets, set A and set B.), or 2) two or more beads distinguished by their fluorescent labels, even if they are bound to oligonucleotides with identical sequences.

8. The term "random bases" is not defined, therefore it is interpreted as any bases.

9. The limitation of claim 32, "fluorescence color ratio incorporated into one or more beads of the bead sets" is interpreted as the fluorescent beads possessing fluorescence dyes with emission spectra at two different wavelengths, which allow measurement of fluorescence ratios for each of the beads.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claims 22-31, 33-37 and 39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Armstrong et al. (Cytometry, vol. 40, pp. 102-108, June 1, 2000; cited in the previous office action), Van Ness et al. (U. S. Patent No. 6,361,940 B1; cited in the previous office action) and Lee et al. (U. S. Patent No. 6,207,379 B1; cited in the previous office action).

A) Regarding claim 22, Armstrong et al. teach a method of detecting SNPs (=alleles) (Abstract) by hybridization, the method comprising

hybridizing a target oligonucleotide to oligonucleotides that are coupled to different bead sets to form a complex (Armstrong et al. teach oligonucleotide probes coupled to fluorescently encoded microspheres (= beads). The probes are hybridized to fluorescently labeled PCR reaction products. For each SNP, four probes were used, with each of the four dNTPs substituted for the variant base located in the middle of the probe, and each probe sequence was coupled to a fluorescently tagged microsphere. Therefore, Armstrong et al. teach four bead sets for each SNP. PCR-amplified genomic DNA (= target oligonucleotide) was labeled with fluorescein, and hybridized to the probes (Fig. 1; page 102, the last paragraph; page 103, first paragraph).); and

assaying the complex for specificity of different alleles (Armstrong et al. teach detecting the complexes by flow cytometry (page 103, second paragraph).).

Regarding claim 23, Armstrong et al. teach separation of the allele-specific hybridization products by flow cytometry (page 103, second paragraph).

Regarding claim 24, Armstrong et al. teach probes specific for each of the variations of the SNPs coupled to different beads (Fig. 1; page 102, the last paragraph; page 103, first paragraph).

Regarding claim 25, Armstrong et al. teach coupling of oligonucleotides specific for different polymorphisms to different bead sets (Fig. 1; page 102, the last paragraph; page 103, first and third paragraph).

Regarding claim 27, Armstrong et al. teach obtaining genomic DNA samples from patients. The sample contained multiple alleles of the following genes: ADRB, APOE, CHRM2, COMT, HTR1B1, HTR1B2, KLK2 and UGT (page 104, first and second paragraphs).

Regarding claim 28, Armstrong et al. teach amplification of the genomic target nucleic acid (page 104, first and fourth paragraphs).

Regarding claim 29, Armstrong et al. teach denaturing of the double-stranded target nucleic acid into single strands (page 102, the last paragraph, continued on page 103; page 104, third paragraph).

Regarding claim 30, Armstrong et al. teach hybridizing each target nucleic acid with four different bead sets, each one of which is complementary to one SNP variant, and detecting the complexes by flow cytometry (Fig. 1; page 103, third paragraph). Therefore, Armstrong et al. teach confirming the sequence of the target oligonucleotide with a second bead set.

Regarding claim 36, Armstrong et al. teach oligonucleotides with perfect sequence match (=homology) (Fig. 1).

Regarding claim 37, Armstrong et al. teach oligonucleotides specific for different alleles coupled to a different bead set (Fig. 1; page 103, first and third paragraphs).

Regarding claim 39, Armstrong et al. teach fluorescent beads (Abstract; page 102, last paragraph; page 103).

B) Armstrong et al. do not teach oligonucleotides with and without spacers.

C) Van Ness et al. teach compositions and methods for increasing specificity of hybridization reactions.

Regarding claim 22, Van Ness et al. teach an array of oligonucleotides immobilized on solid support, each of the nucleotides comprising a specificity spacer (col. 11, lines 53-67; col. 12, lines

1-37; Fig. 26). Van Ness et al. teach that combinations of oligonucleotides with different spacers are used in any reaction involving hybridization, such as genetic screening and amplification reactions (col. 44, lines 59-67; col. 45, lines 1-3). In particular, such reactions include allele-specific PCR (amplification with allele-specific primers; col. 46, lines 27-33), DNA sequencing (col. 47, lines 38-42), PCR (col. 49, lines 63-67) and single-nucleotide primer extension (col. 51, lines 62-67; col. 52, lines 1-5; col. 55, lines 65-67; col. 56, lines 1-14; col. 61, lines 1-40).

Regarding claims 26, Van Ness et al. teach oligonucleotides specific for two different base-pair mismatches, i.e., containing different spacers, coupled to different bead sets labeled with fluorescent labels such as BODIPY, TAMRA or Texas Red. Oligonucleotides specific for the wild-type sequence did not have a spacer (col. 83, lines 10-29).

Regarding claim 27, Van Ness et al. teach polymorphism detection is samples containing CYP2D6 gene with 8 polymorphic sites (col. 97, lines 36-52).

Regarding claim 28, Van Ness et al. teach amplifying the gene fragment containing all of the polymorphisms (col. 98, lines 55-67).

Regarding claim 29, Van Ness et al. teach denaturing the target nucleic acid (col. 98, lines 9-11).

Regarding claim 31, Van Ness et al. teach HLA alleles (col. 63, lines 25-44).

Regarding claim 33 and 34, Van Ness et al. teach the spacer being nucleic acid bases (col. 40, lines 30-41; col. 44, lines 61, 62).

Regarding claim 35, Van Ness et al. teach the spacer in the middle of oligonucleotide sequence (col.. 42, lines 53-56).

Regarding claim 36, Van Ness et al. teach oligonucleotides with perfect sequence homology to their target oligonucleotides (col. 18, lines 39-41, lines 61-63; col. 19, lines 16-18).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used beads coupled to oligonucleotides with and without spacers of Van Ness et al. in the method of SNP typing of Armstrong et al. The motivation to do so, provided by Van Ness et al., would have been that using oligonucleotides with spacers provided increased specificity of primer or probe annealing to target (col. 42, lines 12-34), therefore allowing for accurate determination of allelic sequences.

D) Neither Armstrong et al. nor Van Ness et al. teach oligonucleotides with a spacer where complementary regions of the oligonucleotides flank the spacer and where the complementary regions hybridize with a contiguous sequence on the target oligonucleotide.

E) Lee et al. teach detection of target nucleic acid sequences with diagnostic primers (= oligonucleotides) (Abstract). In one embodiment, the primer consists of a spacer flanked by two regions which are complementary to the target nucleic acid and hybridize with a contiguous sequence to the target (Fig. 2A-2C; col. 5, lines 45-67; col. 6, lines 1-16). Lee et al. teach that the primers are used in detection of alleles, such as HLA alleles (col. 6, lines 31-42).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used the oligonucleotides with spacers of Lee et al. in the method of allele detection of Armstrong et al. and Van Ness et al. The motivation to do so, provided by Lee et al., would have been, as stated by Lee et al.:

"Use of the diagnostic primers of the invention will add extra selectivity to the sequence specific primer method because more than two unique sequences can be used as the selection criteria for the PCR. Thus, the number of separate PCR reactions required for assigning an unknown allele may be reduced which reduces the cost of PCR-SSP testing. Selection of appropriate primers according to the invention will allow resolution of ambiguities that occur in some heterozygous

cases wherein the multi-PCR pattern derived from two different alleles is identical to another pair of alleles.

The use of primers according to the invention allows greater specificity in the recognition of a specific allele or set of alleles by using more than one region of sequence homology to the nucleic acid sequence of interest. Increasing the specific recognition of nucleic acid sequence homology refines the ability to carry out a variety of DNA-based tests. Included among these tests would be HLA tissue typing, detection of genetically inherited diseases, detection of infectious organisms in tissue, or detection of a variety of other markers or conditions based on the presence of a nucleic acid sequence (e.g. for testing the efficacy of a gene therapy technique)." (col. 6, lines 20-42).

12. Claims 32 and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Armstrong et al. (Cytometry, vol. 40, pp. 102-108, June 1, 2000; cited in the previous office action), Van Ness et al. (U. S. Patent No. 6,361,940 B1; cited in the previous office action) and Lee et al. (U. S. Patent No. 6,207,379 B1; cited in the previous office action), as applied to claim 22 above, and further in view of Fulton et al. (Clin. Chem., vol. 43, pp. 1749-1756, 1998; cited in the previous office action).

A) Armstrong et al. teach Luminex-64 microspheres (page 103, fifth paragraph), but do not specifically teach that they possess fluorophores with two different emission wavelengths. Van Ness et al. teach determination of fluorescence ratios for beads with different fluorophores (col. 83, lines 55-61), but do not specifically teach beads which possess fluorophores with two different emission wavelengths. Lee et al. do not teach beads which possess fluorophores with two different emission wavelengths.

B) Fulton et al. teach a set of 64 different Luminex beads, which were bound to two different dyes emitting at two different wavelengths, orange and red. The beads are classified by the flow cytometer based on the ratio of orange to red emission profile (Abstract; page 1749, first and

last paragraphs; page 1750, first paragraph). Fulton et al. teach detection of HLA-DQA1 alleles with the different bead sets (page 1751, third, sixth and seventh paragraphs; page 1753, paragraphs 2-5; page 1754).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used the two-color fluorescent beads of Fulton et al. in the method of allele detection of Armstrong et al., Van Ness et al. and Lee et al. The motivation to do so, provided by Fulton et al., would have been that using the two-color beads allowed analysis of 64 different reactions simultaneously (page 1749, second paragraph) and, as stated by Fulton et al.:

> "The system provides several advantages for analysis of biologically and medically relevant molecules, including speed, economy, and advanced analytical capabilities. The system reduces assay time by performing multiple analyses simultaneously rather than sequentially. The no-wash format of many microsphere-based assays, particularly in the final detection step, is considerably faster than microtiter-based assays that require multiple washing steps to remove excess reagents. In addition, the rapid kinetics of microsphere-based assays allow shorter incubation times than conventional solid phase assays. The reduced assay time also reduces labor costs for performing multiple analyses. Reagent usage for microsphere-based assays is 10- to 1000-fold less than microtiter-based assays. Multiplexing allows unique analysis of molecular interactions that can only be performed in a multiplexed format." (page 1755, second paragraph).

13. No claims are allowed.

Conclusion

14. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Teresa E Strzelecka whose telephone number is (571) 272-0789. The examiner can normally be reached on M-F (8:30-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

TS
March 8, 2005

JEFFREY FREDMAN
PRIMARY EXAMINER
3/11/05